UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/043,933	03/30/98	BALLOUL J	017753-094

021839 HM12/1006
BURNS DOANE SWECKER & MATHIS L L P
POST OFFICE BOX 1404
ALEXANDRIA VA 22313-1404

EXAMINER	
FOLEY,S	
ART UNIT	**PAPER NUMBER**
1648	18

DATE MAILED: 10/06/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/043,933	BALLOUL ET AL.	
	Examiner	Art Unit	
	Shanon A. Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21 and 23-37* is/are pending in the application.

4a) Of the above claim(s) *10-20 and 25-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 21, 23, 24, and 32-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☒ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☒ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

The Group and/or Art Unit of your application has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1648, Examiner, Foley.

Continued Prosecution Application

The request filed on 7/27/00 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/043933 is acceptable and a CPA has been established. An action on the CPA follows.

Upon further review all previous rejections are withdrawn. Applicant's arguments with respect to claim1-9, 21, 23, 24, 32, and 33 have been considered but are moot in view of the new ground(s) of rejection.

Response to Amendment

This is a response to the amendment G, paper No. 17, filed 8/4/00. Claims 1, 32, and 33 have been amended. Claims 34-37 have been added. Claims 1-21 and 23-37 are pending. Claims 10-20 and 25-31 are directed to a non-elected group and have been withdrawn from consideration as previously stated. Claims 1-9, 21, 23, 24, 32-37 are considered. Applicant is reminded to cancel the claims to the non-elected invention.

Double Patenting

Claims 10-20 and 25-31 of this application conflict with claims 10-20 and 25-31 of Application No. 09/506,942. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention

during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1-9, 23, and 24 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 10, 11, and 23-31 of copending Application No. 09/506,942. Although the conflicting claims are not identical, they are not patentably distinct from each other because the polypeptides in the present application are identical to the polypeptides in the divisional application for the prevention or treatment of a papillomavirus infection. Each application states that the identical proteins are expressed from independent expression control elements, which could be accomplished by any vector, such as vaccinia.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 21, and 32-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4, 8, and 32 refer to polypeptides from the early (E6 and/or E7) "region" and the late (L1 and/or L2) "region" of a human papilloma virus. What are these regions? A fragment consisting of 3 amino acids would satisfy the claim requirement of a polypeptide obtained from the early and late "regions". The claims have been interpreted in light of the specification and since the specification does not set forth clear metes and bounds of the intended early and late "regions" of the papilloma virus, the claims are considered to be indefinite.

Claims 2-4, 6-8 refer to polypeptides or proteins "derived" from the E6, E7, L1, IL-2, B7.1. What does "derived" mean? Is the claim referring to a percentage of homology structural components or a similar functional characteristic to the native proteins? Claims 2-4 and 8 have no defined "region" that these polypeptides or proteins could be "derived" from. Therefore, these undefined limitations interfere with the ability of one of skill in the art to reduce the invention to practice.

Claims 5 and 9 are indefinite because it recites an improper Markush group. The applicant is referred to MPEP 2173.05(h) and advised to reformat the claim to read "wherein R is a material selected from the group consisting of A, B, C **and** D" or "wherein R is A, B, C **or** D".

Claim 21 is unclear. The claim recites "a pharmaceutically acceptable carrier allowing its administration by injection". What is "its" referring to, the carrier or the composition? Also, how does the carrier or the composition "allow administration"?

Claims 32-37 refer to nononcogenic "variants" of E6 and/or E7 proteins of a human papilloma virus. What is this "variant" referring to? Is the "variant" a protein, an isolated amino acid, or part of a nucleic acid from E6/E7? A clear definition of what is meant by a "variant" is not provided in the specification in the terms of homologous structural components or similar functionality of other substances that could define a "variant" of E6/E7. Claims 36 and 37 limit the structure of the "variant" by specific deletions that further define a structural characteristic. However, the "variant" substance remains undefined to further limit the metes and bounds of the "variant".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-4, 6-8, and 32-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a genus of proteins or polypeptides "derived" from the E6, E7, L1, IL-2, B7.1 and "variants" of E6 and E7 of a human papilloma virus. The specification does not teach what structural elements of these derivations or variants. The specification reduces to practice only one species within the genus on page 18, line 34 and page 19, lines 4-8, the deletion-modified protein of E7, in which amino acids 21-26 have been deleted and the deletion-modified E6, in which amino acids 111-115 have been deleted. Since the genus embraces a wide variety of possible derivatives and variants of each polypeptide or protein, the single species of

each polypeptide or protein is not seen as representative for the full genus claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 8, 9, 21, 23, and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Stanley et al. in WO 96/29091.

The claims are drawn to a pharmaceutical composition intended for the prevention or treatment of a papillomavirus (HPV) infection comprising a polypeptide from E6 and/or E7 and L1 and/or L2 and a polypeptide having immunostimulatory activity, such as interleukin-12 (IL-12). All of the polypeptides are expressed recombinantly from independent expression control elements. The pharmaceutical composition is administered by injection.

Stanley et al. teaches a papilloma vaccine for the treatment of human papillomavirus infection, see page 4, lines 6-7 and 17-22. The composition comprises at least a substantial part of one of the proteins E1, E2, E4, E6, E7, L1 and/or L2 of HPV types 6, 11, 16, and/or 18, and IL-12, see page 4, lines 29-37, and claims 5, 6, 13, 15. The polypeptides are expressed by independent expression control elements with the use of a recombinant vaccinia virus vector encoding a polypeptide, antigenic fragment, or fusion protein, see page 5, lines 2-8 and claims 7, 8, 13, 16, and 17. Claim 3 further anticipates the use of IL-12 as an immunotherapeutic or as an immunostimulatory vaccine adjuvant. The patent claims clearly state that the expression vector encode at least one papillomavirus protein, clearly encompassing multiple expression vectors,

each expressing a different papillomavirus protein that **are not fused** to each other, see page 6, line 7 and page 11, lines 21-25. In addition, Stanley et al. teaches that the composition is injected, see page 6, lines 28-31 and page 7, lines 7-15. All of the teachings of Stanley et al. anticipate claims 1-5, 8, 9, 21, 23, and 24.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9, 21, 23, 24, 32, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Galloway, Hines et al., and Gajewski.

The claims are drawn to a pharmaceutical composition intended for the prevention or treatment of a papillomavirus (HPV) infection comprising a polypeptide from E6 and/or E7 and L1 and/or L2 and a polypeptide having immunostimulatory activity, such as interleukin-2 (IL-2), and a co-adhesion molecule B7.1.

Galloway teaches a prospect for prophylactic vaccine to treat papillomavirus infections with a composition that includes L1and L2 proteins and therapeutic vaccines that include E6 and E7 proteins from the papillomavirus, see the abstract on page 187. Galloway also teaches that most individuals have antibodies that recognize the capsid proteins, especially L2, see the first paragraph of column 2 on page 189. In addition, rabbits immunized with L1 or L2 conferred protective immunity against the virus, see first full paragraph of column 2 on page 190. Galloway also teaches that L2 and E7 fusion proteins have reduced the number, severity, and

duration of lesions. E7 was found to protect mice from a syngeneic tumor in an MHC-restricted fashion, see the paragraph bridging pages 190-191. Stimulation of the immune response against E6 and/or E7 may be beneficial in clearing tumors, see the next to the last sentence of the second column on page 191. From the teachings of Galloway, one of skill in the art at the time of the invention would have been motivated to combine E6, E7, L1, and/or L2 into a vaccine to treat or prevent a papillomavirus infection. One of skill in the art at the time of the invention would have had a reasonable expectation of success because of the prophylactic properties of L1 and L2 to confer immunity and the treatment of tumors demonstrated by E6 and E7. Galloway does not teach the use of IL-2 and B7.1 to aid in activating the immune response.

Hines et al. teaches that the E7 oncoprotein peptide injected into mice induces a protective cell-mediated response against tumor formation after a challenge with HPV 16-transformed tumor cells in vivo. Immunization with peptides prevents tumor formation. Hines et al also proposes cell adoptive therapy treatment to accelerate tumor regression. This is accomplished by removing a patient's serum and stimulating their lymphocytes in vitro with a peptide, E6 and E7, and a cytokine, IL-2, and returned to the cancer patient as therapy, see the "cellular adoptive therapy" section on page 862-863 and figure 2 on page 863. Hines et al. concurs with Galloway in teaching that the major capsid proteins, L1, from the papillomavirus, see table 1 on page 861, mimicked the conformation of intact virions and were recognized by well-defined type-specific antibodies. Immunologically active virus-like particles used in a prophylactic vaccine would be successful because they are antigenic,, protective in animal models, and lack the viral DNA that would be carcinogenic in the host. Demonstrated again by the teachings of Hines et al., one of skill in the art at the time of the invention would have had a

reasonable expectation of success because of the prophylactic properties of L1 and L2 to confer immunity and the treatment of tumors demonstrated by E6 and E7. Hines et al. does not teach the incorporation of B7.1 to aid in stimulating T cells.

Gajewski teaches that T cells require the participation of one additional "second signal" to secrete IL-2. This "second signal" capable of activating CD4+ and CD8+ T cells to secrete IL-2 is B7.1 and is used as a cofactor for IL-2 production and has been found to be necessary for the production of IL-2. B7.2 is also can also provide costimulator function for IL-2 production of CD4+ cells. Gajewski goes on to teach that the this aspect of cytotoxic T lymphocytes (CTL) would have a practical application in the development of tumor-specific immunotherapy, see the introduction on page 465. Expression of B7.1 human tumor cells can render them better able to stimulate alloreactive CD8+ lymphocytes to produce their own IL-2, see the first paragraph of the discussion section on page 470. The only difference between the claimed invention and the teachings of Gajewski is a direct papillomavirus vaccine that incorporates B7.1 and IL-2 along with the papillomavirus proteins E6, E7, L1 and/or L2.

One of skill in the art at the time the invention was made would have been motivated to combine the teachings of Galloway, Hines et al. and Gajewski to provide a prophylactic and a treatment vaccine that would represent the major antigens of the papillomavirus and with an enhanced ability to stimulate T cells with IL-2 and B7.1. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because of the success taught by Galloway and Hines et al. in preventing papillomavirus infections with a composition that includes L1and L2 and therapeutic vaccines that include E6 and E7 proteins from the papillomavirus. The addition of

IL-2 to a vaccine composition taught by Hines et al. would be advantageous in stimulating T cell response. The importance of stimulating IL-2 was taught by Gajewski as well as the capability of B7.1 to stimulate a T cell response to produce IL-2. Therefore, it would have been prima facie obvious to one skilled in the art at the time the invention was made to combine the teachings of the references to make a successful vaccine for the treatment and prevention of papillomavirus infections.

Claims 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanley et al., Galloway, Hines et al., and Gajewski as applied to claims1-9, 21, 23, 24, 32, and 33 above, and further in view of Munger et al. and Crook et al.

The claims are drawn to an HPV-16 E6 protein modified by a deletion of amino acids 111-116 and an HPV-16 E7 protein modified by a deletion of amino acids 21-26.

See the teachings of Stanley et al., Galloway, Hines et al., and Gajewski above. The references do not expressly teach the claimed mutations.

Crook et al. teaches loss of the wild-type tumor suppressor function is achieved by the expression of HPV-16, see the last paragraph of column 1 on page 547. Crook et al. also teaches that an amino acid mutation in E6 reduces binding to p53 by 94% by deleting amino acids 111-115. Munger et al. teaches that E7 disrupts the retinoblastoma (RB) tumor suppressor gene by forming a complex with RB, see the abstract on page 4099. Munger et al. also teaches that the amino acid sequences necessary to form the complex formation with RB is located at a small stretch of amino acids surrounding the cysteine residue at sequence position 24, see the last 2 sentences of the introduction on page 4099. One of ordinary skill in the art at the time of the invention would have been motivated to utilize the specific deletions taught by the references to

significantly decrease or eliminate tumor suppression in these proteins. The combined references of Stanley et al., Galloway, Hines et al., Gajewski, Munger et al., and Crook et al. render the invention as a whole prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon A. Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on 7:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley
October 4, 2000